Systemic symptoms and systemic infections

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19.1 Approach to systemic symptoms in HIV infection

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HIV infection itself may cause systemic symptoms, such as fatigue, weight loss, night sweats and diarrhoea. However, it must not be assumed that these symptoms are caused by HIV until all possible opportunistic or co-existing disease processes have been excluded. Adherence to this important principle may avoid potentially serious consequences including immune restoration disease when combination antiretroviral therapy (cART) is commenced in the presence of a previously undiagnosed opportunistic infection.

19.1.1 Systemic symptoms

Systemic symptoms such as fever, night sweats and weight loss may be caused by a wide range of disease processes in people with HIV infection, especially those with advanced immunodeficiency. Infections and malignancy are the most common groups of diagnoses in HIV-associated pyrexia of unknown origin, with collagen disorders rarely reported.[1,2]

Most of the studies of pyrexia of unknown origin in HIV disease have come from countries with a high prevalence of tuberculosis (TB) or leishmaniasis, which are less common in the Australian setting.[2-6] A diagnosis is reached in most cases of HIV-related pyrexia,[1] and in most cases the condition is treatable. Non-infective causes, common and rare (e.g. thyroiditis), need to be considered in the differential diagnosis.[7] The effects of cART on the diagnostic spectrum in cases of pyrexia of unknown origin have not been reported but immune reconstitution-related illnesses will be one cause of fever in the setting of recent commencement of cART (see Chapter 22).

19.1.2 Drug reactions

Drug fever (without other manifestations such as skin rash) contributed to 1.7% of all adverse drug reactions in one prospective study of hospitalised inpatients with HIV infection, and needs to be considered as a potential cause of unexplained fever.[8] Drugs commonly used in patients with HIV which have been associated with drug fever include dapsone, sulphamethoxazole/trimethoprim, pegylated interferon, phenytoin, beta-lactams and amphotericin B.

19.1.3 Localising features

In patients with systemic symptoms, such as fever and weight loss, a more careful assessment for localising signs and symptoms should be undertaken. For example, persistent (even mild) headache may be associated with significant central nervous system pathology (such as cryptococcal meningitis) and warrants investigation. Patients with *Pneumocystis jirovecii* pneumonia (PJP) may report fatigue on exertion without breathlessness and may not experience symptoms such as a mild non-productive cough. PJP may also present as a pyrexia of unknown origin. A complete examination, looking particularly for lymphadenopathy, hepatosplenomegaly, abdominal masses, focal neurological deficits, respiratory signs and signs of infective endocarditis should be undertaken. The findings of the examination, in conjunction with knowledge of the degree of immunodeficiency, exposure history (e.g. travel to areas endemic for TB or leishmaniasis) and basic haematological and biochemical testing will direct the sequence of investigations (Table 19.1).

19.1.4 Hierarchy of investigations

As with any investigative approach, the least invasive and cheapest investigations are performed initially, with full blood examination and liver function tests providing useful clues. Standard blood cultures and mycobacterial blood cultures (especially if CD4 cell count is <50 cells/μL) should be taken. Additional investigations are conducted in conjunction with a focused assessment based on localising features (Table 19.1). Serum cryptococcal antigen titre should be measured in those with a CD4 cell count <100 cells/μL. If no clinical lesions are detected and chest radiography is normal, a computed tomography scan of the abdomen may reveal clinically imperceptible lymphadenopathy and provide useful information about the nature of any organomegaly. Unexplained skin lesions should be biopsied and sent for histological examination (including stains for *Bartonella*, fungi and mycobacteria) and microbiology (including fungal and mycobacterial culture). Lymph nodes should be examined by fine-needle aspiration followed by excisional biopsy if non-diagnostic. Bone-marrow biopsy may be the preferred next diagnostic step before excisional biopsy of intra-abdominal or intrathoracic lymphadenopathy is undertaken. Although the yield from liver biopsy for mycobacterial disease is higher than that of bone marrow biopsy,[9,10] significant thrombocytopenia may make liver biopsy less safe. The diagnostic sensitivity and relative safety of bone-marrow biopsy makes it a more useful initial investigation.[11-13] Gallium scanning may localise clinically silent pathology.[14]

19.1.5 Deferral of cART and opportunistic infection prophylaxis

Given the likelihood of diagnosing a significant infection or tumour in an immunodeficient person, cART and prophylaxis for opportunistic infection should be deferred until a definitive diagnosis of the cause of the systemic symptoms has been made and the cause treated. The introduction of prophylaxis for *Mycobacterium avium* complex (not universally recommended

Table 19.1 Features of diseases associated with a systemic febrile syndrome

Disease	Risk group	Symptoms/history in addition to fevers and weight loss	Signs	Investigations
Pneumocystis jirovecii pneumonia (PJP)	CD4 cell count <200 cells/μL No PJP prophylaxis	Fatigue Cough Dyspnoea	Exertional oxygen desaturation Auscultation may reveal rales or be normal	Elevated A-a gradient on ABG Diffuse infiltrates on chest x-ray Organism identified in induced sputum
Disseminated *Cryptococcus neoformans*	CD4 cell count <100 cells/μL	Headache Skin rash Cough	May have none May have meningism and/or altered mentation	Serum cryptococcal antigen Blood culture CSF examination (India ink stain, cryptococcal antigen, culture)
Mycobacterium avium complex (MAC)	CD4 cell count <50 cells/μL No MAC prophylaxis	Drenching night sweats Cough Diarrhoea Lethargy Nausea Vomiting	Hepatosplenomegaly Palpable intra-abdominal mass (intra-abdominal lymphadenopathy)	Anaemia Elevated alkaline phosphatase Para-aortic lymphadenopathy (CT scan) MAC culture using special blood-culture systems AFB identified by culture and histology of biopsy of lymph node, bone marrow or liver
Cytomegalovirus	CD4 cell count <50 cells/μL	Visual symptoms Diarrhoea Abdominal pain Non-focal/focal neurological symptoms	Hepatosplenomegaly Retinitis Abdominal tenderness (in colitis) Rapid neurological deterioration (encephalitis/ventriculitis)	Retinal examination Detection of CMV antigens or DNA by PCR Biopsy of bowel revealing CMV inclusions and a neutrophilic inflammatory response
Lymphoma	Any CD4 cell count, usually <200 cells/μL	Variable, may include lymphadenopathy, extranodal masses, tissue infiltration, night sweats, fever, weight loss	May have hepatosplenomegaly, lymphadenopathy, other masses	Biopsy of lymph node or extranodal mass or bone marrow Cytology on CSF examination Fine-needle biopsy of lymph node may be diagnostic; if not, progress to excisional biopsy
Drug reaction	Recent drug introduction (especially cotrimoxazole, abacavir, an NNRTI, an anticonvulsant) More advanced HIV disease	Possible rash	Rash or nil	Possible eosinophilia or abnormal liver function
Disseminated *Mycobacterium tuberculosis*	Any CD4 cell count History of exposure, travel to or residence in endemic area. Prior Mantoux test >5 mm without treatment of latent infection, or anergic and recent exposure to TB	Pulmonary symptoms Other symptoms dependent on location of extrapulmonary disease	Pulmonary signs Lymphadenopathy Hepatosplenomegaly	Sputum sample for AFB stain and culture Mycobacterial blood culture Biopsy of lymph node, bone marrow or liver for AFB stain and culture

Table 19.1 Features of diseases associated with a systemic febrile syndrome - continued				
Disease	**Risk group**	**Symptoms/history in addition to fevers and weight loss**	**Signs**	**Investigations**
Immune reconstitution syndromes	Recent introduction of cART with or without increase in CD4 cell count	Localising symptoms depending on primary disorder	Localising signs depending on primary disorder	Diagnostic tests if undiagnosed opportunistic infection (e.g. biopsy of enlarged lymph node)
Retroviral rebound syndrome	Recent cessation of cART	Symptoms of primary HIV infection	Rash Pharyngitis Lymphadenopathy Meningitis	No specific diagnostic test Features consistent with primary HIV infection Exclude opportunistic infection
Endemic mycoses (histoplasmosis and coccidio-domycosis)	CD4 cell count <150 cells/µL Travel to or residence in endemic area	Cough Dyspnoea Diarrhoea	Hepatosplenomegaly Lymphadenopath	Sputum, blood or bone marrow culture Blood smears or urine antigen test for *Histoplasma* *Coccidioides* serology
Visceral leishmaniasis	CD4 cell count <200 cells/µL Travel to or residence in endemic area	Skin lesions Diarrhoea Cough Abdominal pain	Hepatosplenomegaly Diarrhoea	Pancytopenia Blood smear examination Bone-marrow biopsy Serology
Other possible causes of systemic symptoms include: infective endocarditis, disseminated Kaposi's sarcoma, other non-tuberculous mycobacteria, bartonellosis, nocardiosis, aspergillosis, disseminated carcinoma, bacteraemia (e.g. with pneumococcal pneumonia, *Salmonella* spp.), *Penicillium marneffei*, bacterial enteritis, hepatoma in persons with viral hepatitis co-infection, Castleman's syndrome.				
A-a = alveolar–arterial; ABG = arterial blood gas; AFB = acid-fast bacilli; CMV = cytomegalovirus; CSF = cerebrospinal fluid; CT = computed tomography; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; PCR = polymerase chain reaction.				

in the cART era[15]) or TB may lead to drug-resistance in the setting of undiagnosed, disseminated mycobacterial infection; cotrimoxazole prophylaxis for PJP may reduce the utility of bacterial cultures; and the introduction of cART may be associated with significant immune reconstitution disease.

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19.2 Uncommon infections to consider in the presence of constitutional symptoms

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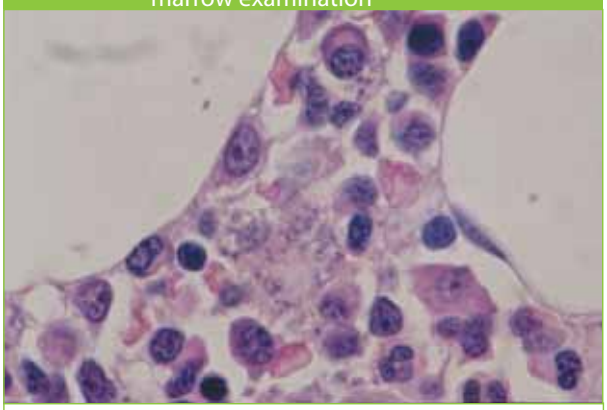
There are several uncommon infections, often presenting with non-specific constitutional symptoms, that may occur in people with HIV in Australia. Demographic features, travel history, the clinical history and signs on presentation provide the stimulus to consider and rule out the following conditions. Several conditions which may present with systemic illness relevant to the care of patients with HIV outside Australasia such as malaria, babesiosis, Chagas' disease and *Paracoccidioides* are not described in this chapter. Several infections which cause systemic symptoms, including TB, are described in other chapters.

19.2.1 Leishmaniasis

Leishmania spp. produce a variety of clinical entities including visceral, cutaneous and mucocutaneous forms. Although considered rare in Australia, it is the second most common protozoan infection encountered in people with HIV worldwide[1] and is endemic in over eighty countries. Infection in humans occurs when parasitised female sandflies regurgitate the parasite's flagellated promastigote stage when feeding on a human host. Phagocytised by macrophages, these promastigotes then transform into the nonflagellated amastigote form, which then divides by binary fission. Recently there has been increasing evidence for an important anthroponotic cycle in injecting drug users, where amastigotes are directly transmitted by reusing injection equipment.[2]

Two factors have traditionally been thought to influence the development of disease: the virulence factors of the parasite itself, and the immune response of the host. However, strains otherwise considered nonpathogenic may cause disease in patients with HIV.[3] Some data suggest that *Leishmania* infection itself may act as a cofactor in the pathogenesis of HIV disease people with co-infection.[4] Given the interaction between host immune function and development of clinical disease, the use of cART would be expected to reduce the incidence of visceral leishmaniasis (VL); in fact, this decrease has been apparent in areas in which these treatments are available.[5]

Image 19.1 Leishmania organisms identified on bone marrow examination



Source: Lloyd A, University of NSW, Sydney, NSW. Used with permission.

Clinical presentation

Clinical disease may present as either primary infection in people returning from endemic areas or reactivation of latent disease. In both situations, disease is seen most commonly in advanced immunosuppression with CD4 cell counts <200 cells/μL. VL, predominantly caused by *L. infantum*, is the most common clinical form seen in people with HIV. In contrast to HIV-negative patients, exclusively cutaneous leishmaniasis is rare, occurring in only 2-3% of those with HIV and leishmaniasis. Cutaneous involvement, however, often accompanies visceral disease.[6] Skin lesions present as papules, nodules or plaques with a central depression and raised indurated border. Secondary bacterial infection and regional adenopathy often accompany these lesions.[1] Mucocutaneous leishmaniasis has been described with lesions especially affecting the nasal, buccal and pharyngeal areas.[7] Post-kala-azar dermal leishmaniasis may also occur as an immune reconstitution disease.[8]

In VL the target organs most commonly involved are bone marrow, liver, spleen, lymph nodes and, in people with HIV infection, the gastrointestinal[9] and respiratory tracts,[10] and occasionally the myocardium and adrenals.[11] Three-quarters of all patients present with the classical triad of fever, pancytopenia and hepatosplenomegaly. Asthenia and significant weight loss are seen in up to 90% of people with HIV.[1] Diarrhoea, dysphagia, abdominal pain and cough may also be presenting symptoms depending upon the viscera involved. The differential diagnosis of VL includes mycobacterial diseases, histoplasmosis, coccidioidomycosis, disseminated cytomegalovirus (CMV) infection and lymphoma.

In any episode of VL, more than 50% of all patients will be diagnosed with a concomitant opportunistic pathogen, most commonly oesophageal candidiasis, extrapulmonary TB, PJP or disseminated CMV.[12]

Diagnosis

Diagnosis of VL requires demonstration of parasites in blood or tissue. Amastigotes have been demonstrated by simple microscopic examination in peripheral blood preparations in a high proportion (53%) of patients with HIV infection and VL,[13] with detection increased to 67% with culture of buffy coats in specialised media.[14] This noninvasive method (use of peripheral blood) may permit a simple and rapid diagnosis in people with HIV. Polymerase chain reaction (PCR) is an emerging alternative method of diagnosis with increasing experience of its use in populations with HIV.[15] Stained splenic aspirate preparations are considered the most sensitive method for parasite detection, with detection rates of >90%, but experience with this technique in non-endemic areas is lacking. Bone-marrow biopsy remains a safe alternative for most patients, despite its lower sensitivity of 70%.[16]

Although indirect, immunofluorescence and enzyme-linked immunosorbent assays are commercially available, up to 40% of

people with HIV and VL have no detectable antibody.[17,18] More sensitive serological in-house assays, which have been developed in areas of high prevalence, can diagnose 90% of cases.[19] The serological response may be related to the type and time of infection. Reactivation, where latent infection occurred before immunosuppression, results in detectable antibody. Primary leishmaniasis infection occurring after immunosuppression is associated with the absence of antibody.[20]

Management

The choice of first-line therapy in people with HIV was based on standard leishmaniasis treatment, which has traditionally been either pentavalent antimonial salts or amphotericin B. Both agents cause significant toxicity. Modern alternatives include liposomal amphotericin B and miltefosine. Specialist consultation should be sought before initiating treatment. Response to treatment is generally poor. Antimonial salts have largely been replaced by liposomal amphotericin, although the cost of this preparation limits its use in many endemic areas.

Patients with HIV and VL have a high rate of relapse (90% at 12 months).[21] Mortality is high. One study reported that 19% of patients with HIV died during their first episode of VL, with only 60% surviving one year,[21] reflecting the advanced immunosuppression and concomitant opportunistic infections seen in these people. Relapses appear to be related to the higher parasite burden that occurs in those with HIV, but may also represent the development of drug-resistant forms.[2] Therapies used in the treatment of relapses include antimonial compounds in combination with allopurinol, aminosidine or interferon gamma and pentamidine.[2] There are currently no data that demonstrate the usefulness of azole treatment in patients with HIV and VL, and its use in the treatment of cutaneous leishmaniasis in immunocompetent individuals has been disappointing.[22] Miltefosine, a phosphocholine analogue, is a new oral agent that has shown promising results in both adults and children. The agent is not Food and Drug Administration or Therapeutic Drugs Administration approved. This drug is effective against VL but is expensive and teratogenic, so it cannot be used to treat women of childbearing age. There is a theoretical risk of resistance developing quickly to it, if it is not used in combination with other drugs. Miltefosine is registered in India for first-line treatment of VL, and in Europe for treatment of VL in patients with HIV co-infection, especially in those patients unresponsive to other treatments.[23]

Treatment for cutaneous leishmaniasis in immunosuppressed people should follow the same criteria as for visceral forms of the infection, owing to the risk of later dissemination.

Prophylaxis

Relapses are common. Pentavalent antimony given monthly has been shown to be successful in the prevention of relapses in people with HIV infection,[24] but its use is limited by toxicity. Pentamidine, liposomal amphotericin B, allopurinol and itraconazole have all been tried, but have been shown to be ineffective.[2]

19.2.2 Coccidioidomycosis

Coccidioidomycosis is also known as San Joaquin Valley fever or Valley fever. It is caused by *Coccidioides immitis.* The environmental reservoir for *C. immitis* is the alkaline soil of desert areas and *C. immitis* is endemic in the south-western USA, northern Mexico and certain areas in Central and South America.[25]

Similar to *Histoplasma capsulatum*, it is a thermally dimorphic fungus. The usual route of acquisition of *C. immitis* is inhalation, which may be facilitated by conditions that favour fungal dispersal such as earthquakes, dust storms and earth excavation.[26] In immunodeficient people, approximately 50% of cases are diagnosed in non-endemic areas and result from reactivation of previous infection.[27]

Infection is asymptomatic in half of immunocompetent individuals, with the other half experiencing self-limiting acute respiratory symptoms. There are no published cases of coccidioidomycosis in the setting of HIV in Australia.

Clinical presentation

Most immunodeficient patients with *C. immitis* have a subacute presentation with symptoms lasting weeks to months and consisting of fever, weight loss, fatigue, night sweats, cough, chest pain and dyspnoea.[25] Pulmonary disease is found in 80% of patients, and although disseminated disease is recognised in only 15% of these cases, it is demonstrated at autopsy in most patients.[28] Dissemination may occur to any organ; common sites include the central nervous system, lymph nodes, liver, skin and bone.[27] Meningitis secondary to *C. immitis* presents with headache, fever and confusion.

Diagnosis

Coccidioidomycosis is diagnosed by fungal staining or culture of sputum, bronchoalveolar lavage and skin lesions; however, it is rarely isolated from blood.[27] Laboratory staff should be informed if a patient's travel history suggests *C. immitis* as a possible diagnosis, as special precautions are necessary in the laboratory. Serological testing is useful, especially when seroconversion is demonstrable.

Management

Coccidioidomycosis in the immunodeficient host is a life-threatening illness and amphotericin B (0.5-0.7 mg/kg/day) is considered the initial treatment of choice. For meningitis, fluconazole is preferred. However, response to treatment is disappointing, with mortality of 70% in the setting of diffuse pulmonary involvement and 90% in those with meningitis. Fluconazole and itraconazole are appropriate for milder illness and maintenance therapy. Clinicians need to be aware of potential drug interactions between azoles and other therapeutic agents including antiretroviral drugs. Guidelines for the treatment of coccidioidomycosis have been published;[29] nevertheless, expert advice should be sought in all cases.

Prophylaxis

The role of prophylaxis is uncertain and most authorities do not recommend primary chemoprophylaxis.

Discontinuing maintenance therapy

There is currently no evidence to support discontinuation of maintenance therapy in patients with immune restoration following cART. However, therapy for at least one year is recommended.[30] Even with secondary prophylaxis immune reconstitution disease has been reported.[31]

19.2.3 Histoplasmosis

Although rarely diagnosed in Australia, histoplasmosis remains an important opportunistic infection to be considered in HIV, as it is a common endemic mycosis diagnosed worldwide in people with HIV infection.[25] The causative agent for histoplasmosis is *H. capsulatum*, a thermally dimorphic fungus endemic in areas of North and Latin America. The environmental reservoir for *H. capsulatum* is rich, moist soil, especially that contaminated by bird or bat guano. The usual route of acquisition of *H. capsulatum* is inhalation of microconidia or hyphal elements from contaminated environments, with conversion to the budding-yeast form occurring in the lungs. In immunocompetent individuals, infection is either asymptomatic or it takes the form of a self-limited flu-like illness. *H. capsulatum* infection is thought to be controlled by the development of antigen-specific CD4 T lymphocyte-mediated immunity.

Histoplasmosis occurs in 2-5% of patients with advanced HIV disease from endemic areas in the USA, and in up to 25% of those from selected cities in endemic areas (Indianapolis, Kansas City, Memphis and Nashville).[32,33] In areas such as Europe and Australia, histoplasmosis is recognised in less than 1% of patients with HIV disease.[25,34] though it does appear to be present in both Australia and the Asia Pacific region.[35,36]

Clinical presentation

Histoplasmosis in people with HIV infection generally causes disseminated disease and is rarely seen at CD4 cell counts >150 cells/μL.[37] Most patients have a subacute presentation with constitutional symptoms including fever, weight loss and fatigue, although fulminant illness has also been described.[25] Respiratory symptoms of cough or dyspnoea occur in half of all patients.[25] Nodular or interstitial infiltrates are seen on chest x-ray. Hepatosplenomegaly and lymphadenopathy occur commonly, and gastrointestinal involvement causing diarrhoea, abdominal pain, bleeding, intestinal obstruction and perforation occurs in approximately 10% of cases. Skin manifestations, including pustular, follicular, maculopapular and papulonecrotic lesions, may be seen. A septic-shock-like syndrome, associated with late diagnosis, occurs in approximately 10% of patients and carries an extremely poor prognosis. The central nervous system is involved in 10-20% of cases and may manifest as focal cerebral granulomata, lymphocytic meningitis or diffuse encephalitis.[25] Anaemia, leukopenia and thrombocytopenia suggest bone-marrow involvement. Histoplasmosis may also present as an immune reconstitution disease.[38]

Diagnosis

H. capsulatum may be isolated in cultures from blood, bone-marrow aspirate, biopsy material and respiratory secretions, but, in most patients, cultures will take two to four weeks to become positive. Direct examination of blood or bone-marrow smears may give more rapid results, although blood smears may be positive in only half of all cases.[39] Detection of *Histoplasma* antigen in urine and other body fluids provides a rapid, sensitive and specific diagnostic method, but is currently unavailable in Australia. Antibody testing and skin testing are not useful for the diagnosis of *Histoplasma* in the setting of HIV.[40]

Management

Treatment of histoplasmosis in patients with advanced HIV disease includes an induction phase, followed by lifelong maintenance to prevent relapse. Amphotericin B (0.7-1 mg/kg/day) or liposomal amphotericin B 3 mg/kg/day) is considered the initial treatment of choice for patients with life-threatening illness or neurological involvement. Remission occurs in 80% of treated individuals. In the setting of progressive renal impairment, the new lipid formulations of amphotericin B are useful. Amphotericin B should be given for one to two weeks, followed by treatment with itraconazole (200 mg twice a day) for ten weeks. Itraconazole (200 mg twice daily) or fluconazole (800 mg daily) for 12 weeks are effective induction therapy for patients with mild-to-moderate disease, not requiring hospitalisation.[41] Clinical response may be slower with itraconazole compared with amphotericin B, supporting the use of amphotericin B as initial therapy.

Maintenance therapy with itraconazole (200 mg/day) or amphotericin B (50-100 mg weekly) is highly effective in preventing relapses.[42] Fluconazole, even at high doses, has been associated with a higher relapse rate and is regarded by most clinicians as second-line therapy.[43] Ketoconazole has been shown to be ineffective for maintenance therapy and is not recommended. Histoplasmosis meningitis should be treated with amphotericin B or fluconazole. Itraconazole is not recommended for induction or maintenance for histoplasmosis meningitis because of poor penetration of the cerebrospinal fluid. Induction treatment is recommended with amphotericin B (0.7-1 mg/kg/day) and maintenance therapy with fluconazole (800 mg/day). Liposomal amphotericin B 3 mg/kg/day) may be considered in those who do not respond to amphotericin B and fluconazole.

Prophylaxis

The role of prophylaxis is uncertain; however, there is evidence that itraconazole at 200 mg/day may prevent disease in patients in endemic areas with CD4 cell counts of less than 100 cells/μL.[44]

Discontinuing maintenance therapy

It is likely that secondary prophylaxis may be discontinued in those who have had a strong and sustained improvement in their CD4 cell count following commencement of cART.[45]

19.2.4 *Bartonella* infections

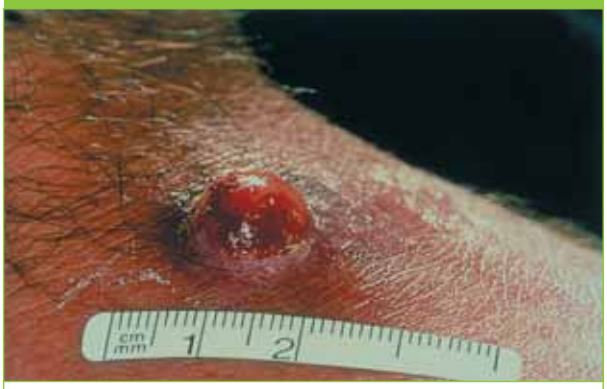
Bartonella species are vector-transmitted, blood-borne, intracellular, gram-negative bacteria from the family *Bartonellaceae*. *Bartonella* spp. have been shown to induce angiogenesis by causing the proliferation and migration of vascular endothelial cells in the host.[46] *Bartonella quintana* is the causative agent for trench fever, an illness characterised by fever, rash, bone pain and splenomegaly. Transmitted by the human-body louse, the illness was common in World War I and has recently re-emerged in marginalised populations, including people with HIV infection, in the USA.[47] *B. henselae* causes cat-scratch disease, an illness of children and young adults which is characterised by painful, regional lymphadenopathy. Cat-scratch disease may persist for weeks or months, but is usually self-limiting. In the immunosuppressed patient, cat-scratch disease is usually more widespread and may be life-threatening. *B.quintana, B. henselae* and *B. elizabethae* have been identified as causative agents of human endocarditis.[48] Members of the cat family are the major reservoir for *B. henselae*.

Clinical presentation

Bartonella infection is rare in people with HIV infection. There are four major presentations: bacillary angiomatosis,

peliosis hepatis, extracutaneous dissemination and bacteraemia. Most cases occur in patients with a CD4 cell count <50 cells/µL and a prior AIDS-defining illness. The most common manifestation is bacillary angiomatosis (caused by either *B. henselae* or *B. quintana*).[49] The cutaneous lesions are pinkish or red papules that may enlarge, become nodular and sometimes ulcerate. These skin lesions may be indistinguishable from Kaposi's sarcoma (KS), reinforcing the importance of biopsy in the diagnosis of *Bartonella* and KS lesions.[50] Hepatic involvement (peliosis hepatitis) presents as fever, abdominal pain and hepatomegaly with or without skin lesions and is caused by *B. henselae*. Numerous blood-filled spaces are demonstrated on liver biopsy. Bacteraemia with systemic symptoms including fever, weight loss and malaise may resemble disseminated *Mycobacterium avium* complex infection. Infection of long bones (almost always due to *B. quintana*) manifests as bone pain and lytic lesions on x-ray. *Bartonella* endocarditis (caused by *B. quintana, B. henselae* and *B. elizabethae*) has rarely been described in the setting of HIV infection.

Image 19.2 Bacillary angiomatosis



Source: Allworth AM, Bowden FJ. HIV and bacterial infections. In: Stewart G, editor. Managing HIV. Sydney: Australasian Medical Publishing Company; 1997:112.

Diagnosis

Biopsy of involved tissue reveals characteristic histological changes with proliferation of small, capillary-sized blood vessels lined by cuboidal endothelial cells in involved skin, lymph nodes or bone, and thin-walled peliotic spaces in the liver. Dark-staining bacilli are visible on silver stain; however, biopsies are not always diagnostic. Definitive diagnosis relies on organism isolation. *Bartonella* spp. are not easily cultured and the ease of isolation may be strain dependant.[51,52] Molecular methods, such as PCR, are becoming increasingly used to identify organisms by characterising 16S ribosomal RNA or other gene sequences.[53]

Management

A prolonged course of a macrolide (either azithromycin 500-1000 mg daily or erythromycin 500 mg every six hours) or doxycycline (100 mg twice a day) alone, or in combination with rifampicin, or gentamicin, is the treatment of choice based on limited data.[54] Treatment for eight to 12 weeks is recommended for those with isolated bacteraemia or bacillary angiomatosis. If relapse occurs, a longer course of therapy should be given. Patients with other manifestations of the infection should be treated for at least three months, and may require indefinite therapy.

19.2.5 Parvovirus

Parvovirus B19 is a non-enveloped, single-stranded DNA virus of the family *Parvoviridae*. It is the only parvovirus thought to be pathogenic in humans. Transmitted by respiratory secretions and contaminated blood or blood products,[55,56] it is the aetiological agent for erythema infectiosum (fifth disease), a common self-limited disease of childhood, characterised by fever and rash. In patients with an underlying haematological disorder, infection with parvovirus B19 may cause a transient aplastic crisis,[57] and infection in utero may result in foetal death, hydrops foetalis or congenital anaemia.[58] In immunocompromised patients, infection with parvovirus B19 may lead to red cell aplasia and chronic transfusion-dependent anaemia,[59] and less commonly to pancytopenia.[60]

Parvovirus B19 is highly tropic to human bone marrow and uses the cell-surface receptor called globoside,[61] (the blood group P antigen) to gain entry to the cell. This receptor is expressed on early erythroid progenitor cells, megakaryocytes, endothelium, foetal and placental cells, and myocardium. Genetic polymorphisms, which result in the absence of this P antigen, are most common in Japan, Finland and Sweden and provide genetic resistance to infection with parvovirus B19.[62]

Clinical presentation

People with HIV and chronic parvovirus B19 infection usually present with a red-cell aplasia and chronic anaemia.[63] Thrombocytopenia, pancytopenia, vasculitis, arthritis and hepatitis have also been described.[64,65] At diagnosis, CD4 cell counts vary.[66,67] There may be a significant lag period between development of anaemia and diagnosis, with one case series reporting a range of two to nine months before chronic B19 infection was diagnosed.[67] As with many other opportunistic infections immune restoration disease has been described.[68]

Diagnosis

Diagnosis is made by the demonstration of typical morphological changes in bone-marrow smears, including severe erythroid hypoplasia with giant and dystrophic proerythroblast,[67] and the detection of parvovirus DNA in blood or bone marrow using a PCR assay. Testing for parvovirus Immunoglobulin (Ig)G and IgM antibodies is not useful, as these antibody responses are usually absent or transient.[69]

Management

In addition to immune restoration with cART, intravenous immunoglobulin therapy may be effective in immunosuppressed patients with persistent parvovirus B19 infection, leading to resolution of the associated red-cell aplasia even when such aplasia is long-standing.[70] The recommended dose is 400 mg/kg intravenously daily for five or ten days. A maintenance infusion of 400 mg/kg is administered monthly to prevent relapse. Hydrocortisone may be given to reduce the incidence of adverse effects of the infusion. In patients with HIV, maintenance therapy appears critical, as single-course therapy does not provide a durable response.[71] Immediately after initial immunoglobulin therapy, parvovirus B19 DNA decreases below the limits of detection of the assay; however, it returns within three to six weeks, leading to further episodes of anaemia.[66] Successful treatment of B19-induced, transfusion-dependent anaemia has been reported in two cases following the introduction of potent antiretroviral therapy.[72,73] After six to seven years of regular transfusions, these patients did not require further blood transfusions, co-incident with a reduction

in levels of parvovirus DNA in blood. It is unclear if eradication of parvovirus B19 occurs. Recently, neutralising monoclonal antibodies directed against B19 proteins have been developed, and these may play an important role in therapy in the future.[74]

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